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EVANS SYNDROME IN A PATIENT WITH COVID-19

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Evans syndrome (ES) is a rare condition characterized by the combination of autoimmune hemolytic anemia and immune thrombocytopenia (ITP). While the precise pathophysiology is not entirely understood, it is believed that dysregulation of the immune system is a primary contributor to the condition. ES has been observed in viral infections including hepatitis C, cytomegalovirus, varicella-zoster, and Epstein-Barr viruses (1-4). Initial cases of coronavirus disease 2019 (COVID-19) were first described in early December 2019 and has now spread to a global pandemic. While knowledge about COVID-19 continues to evolve, clinicians have reported hematologic complications associated with the virus. Presence of lymphopenia has been commonly reported in about 35-40% of cases and appears to be associated with development of acute respiratory distress syndrome (5-7). Thrombocytopenia and coagulopathies, including disseminated intravascular coagulation, have also been reported in cases of COVID-19 which were associated with more severe disease (8, 9). Here, we present the first case, to our knowledge, of COVID-19-associated ES and discuss its unique management issues.

A 39-year-old man presented to the emergency department in late March of 2020 with one day of hemoptysis and epistaxis in the setting of sore throat, productive cough, fevers, chills, and dyspnea lasting about one week. On evaluation, he was found to be

febrile, tachycardic, and tachypneic. Physical exam was notable for dried blood in the oropharynx and nares, as well as a blood blister in the mouth. He had no petechiae, ecchymoses, or rash. Labs demonstrated a leukocyte count of 11,000 cells/µL, hemoglobin of 15.6 g/dL, and platelet count of 3,000 cells/µL. Neutrophil count was 8700 cells/µL, and lymphocyte count was 1700 cells/µL. Hemolysis labs were negative, and there were no schistocytes nor microspherocytes on peripheral blood smear. There was no infiltrate on chest x-ray. Rapid PCR assay for COVID-19 later resulted positive.

On admission, the patient developed worsening bleeding with hematemesis, melena, and hematochezia, associated with a hemoglobin decrease to 6.4 g/dL. Intravenous proton pump inhibitor therapy was initiated, as well as daily intravenous immunoglobulin (IVIG) therapy for presumed ITP secondary to COVID-19. Glucocorticoids were not administered as organizations such as the Centers for Disease Control (CDC) and World Health Organization (WHO) recommended against the use of glucocorticoids in COVID-19 patients (10, 11). On day five, platelet count recovered to 52 cells/µL with resolution of bleeding. By day 6, platelets were 308 cells/µL, hemoglobin was stable at 7.6 g/dL, and the patient was discharged.

Four days after discharge, the patient returned to the hospital with extreme weakness and fatigue, intermittent fever, and cough without bleeding. Hemoglobin was 6.0 g/dL with a normal platelet count. Labs showed a reticulocyte count of 22%, LDH of 947 U/L, elevated fibrinogen, haptoglobin < 20 g/L, and positive direct Coombs test (3+), concerning for new immune-mediated hemolytic anemia. Peripheral blood smear was notable for microspherocytes, nucleated RBCs, and reticulocytes (Figure 1). Coupled with his recent history of ITP, his clinical picture raised concern for ES versus

immune hemolytic anemia secondary to IVIG. Once again, corticosteroids were avoided in the setting of COVID-19 infection, and IVIG therapy was re-initiated. Meanwhile, the patient continued to have low grade fevers with lower extremity weakness and hypoxemia requiring 2L oxygen. After a second dose of IVIG, he developed a left popliteal deep venous thrombosis for which he was started on therapeutic heparin. His hemoglobin eventually stabilized at 7.0 g/dL with robust reticulocyte response. IVIG was discontinued with concern for its contribution to macrovascular thromboembolism. Four weeks after discharge, blood counts showed hemoglobin of 11 g/dL and 505 platelets/μL.

The pathogenesis and management of ES in the setting of the inflammatory milieu of COVID-19 has not been previously described and represents a unique challenge in clinical management. The exact pathophysiology of ES is not fully elucidated but studies suggest the intersection of autoimmunity and predisposing immune dysregulation is involved. Several proposed mechanisms of autoimmunity have been described, including activation of Bruton's tyrosine kinase and overexpression of cytokines (12, 13). Evolving accounts of COVID-19 have demonstrated a pro-inflammatory state with lab abnormalities such as elevated D-dimer, lactate dehydrogenase, C-reactive protein, and ferritin. Case series from China demonstrated higher plasma levels of cytokines in critically ill patients (14). Taken together, dysregulation of the immune system in COVID-19 infection could create favorable conditions for the development of ES.

The mainstay therapy for ES is typically immunosuppression, including corticosteroids. However, the routine use of corticosteroids in COVID-19 patients is not

recommended outside another indication such as shock or obstructive lung disease, according to established guidelines from the WHO, CDC, and Infectious Disease Society of America (10, 11, 15). The basis of this recommendation is founded on analysis from previous viral outbreaks. Retrospective data from the Middle East Respiratory Syndrome (MERS) outbreak have associated steroid therapy with increased mortality and delayed clearance of viral RNA (10). Meta-analysis of steroid use in Severe Acute Respiratory Syndrome (SARS) has been associated with harm, and systematic review of corticosteroid use in influenza patients was associated with increased mortality (11). Thus, alternatives to corticosteroids were used to manage our patient with ES. IVIG, both diagnostic and therapeutic in this case, was used to treat our patient's thrombocytopenia. Thrombopoietin receptor agonists could also be considered in this scenario, as combination of these agents may be useful if platelet rebound is insufficient. It is difficult to know if autoimmune hemolytic anemia in our patient is related to IVIG or underlying immune dysregulation from COVID-19. Nonetheless, treatment options are limited for patients with COVID-19 in this context, and further data is needed to guide the use of immunosuppression in patients with autoimmune complications of coronavirus.

Based on the case above, we propose a framework for COVID-19 patients with hematologic dysfunction that addresses the acuity of bleeding, avoidance of immunosuppression, and support for both platelet and anemia components of ES. Until more data emerges on the use of corticosteroids in setting of COVID-19, avoidance of corticosteroids should be considered in autoimmune hematologic diseases in COVID-19 patients in favor of alternative therapies.

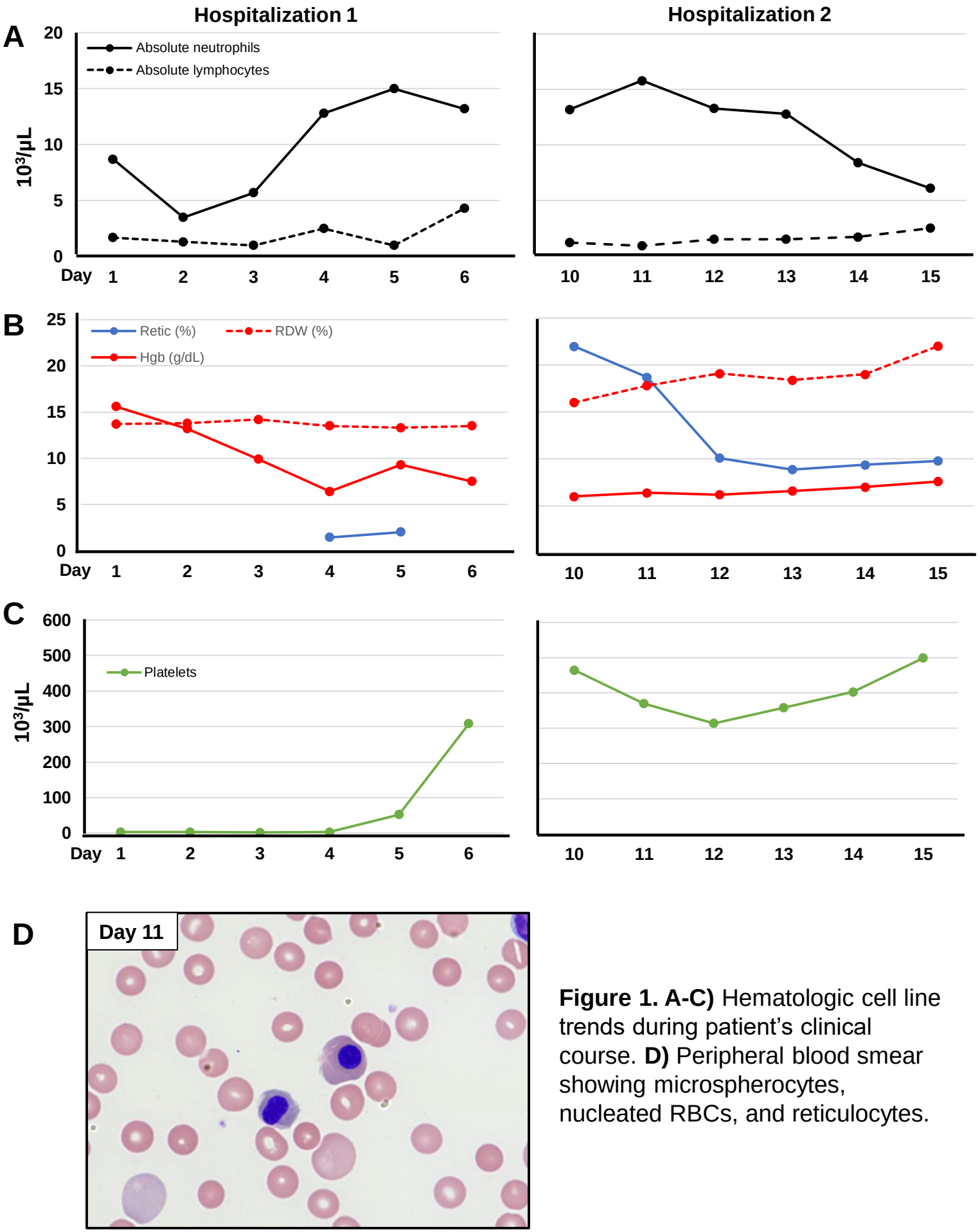

Figure 1. A-C) Hematologic cell line trends during patient's clinical course. **D)** Peripheral blood smear showing microspherocytes, nucleated RBCs, and reticulocytes.